Ambulant Myocardial Ischemia and Its Prognostic Implications

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Recently, unrecognized or silent myocardial ischemia has generated considerable interest. While not a new topic, silent ischemia was originally used in the context of asymptomatic or latent coronary artery disease when ischemic-type ST-segment depression was found on exercise electrocardiograms in totally asymptomatic patients. However, in the mid-1970s, when high-quality ambulatory ECG monitoring became available, many patients with coronary artery disease and relatively stable angina had frequent episodes of asymptomatic, ischemic-type ST-segment depression during daily life.\(^1,2\) Surprisingly, these "silent episodes" occurred at relatively low activity and heart rate levels compared with data from treadmill exercise tests for the same patients.\(^2,3\) These results suggested that changes in myocardial oxygen supply, as well as demand, may be responsible for ambulant ischemia. Mental stressors, cigarette smoking, and other inciting activities were identified.\(^4-6\) Similar ST-segment changes were also observed in patients hospitalized for unstable angina.\(^7-9\) The meaning of painless ST-segment depression in these patients was debated until studies using other independent techniques, such as positron tomography, coronary sinus oxygen saturation, radionuclide angiograms, and hemodynamic monitoring,\(^5,6,10\) confirmed that asymptomatic ST-segment depression was indeed most likely due to transient myocardial ischemia. These studies also suggested that the ECG signal probably underestimated the true frequency of ischemia in these patients,\(^4,6\) and it has become accepted that ambulant ischemia, most of which is silent, is very common in patients with angina pectoris. Additional studies confirmed that ambulant ischemia occurred in patients with other clinical forms of coronary artery disease ranging from those patients who were totally asymptomatic to those who were post-myocardial infarction.\(^11-15\)

Recently, a characteristic daily variation in the frequency and duration of ambulant ischemic episodes has been documented. This variation is the same as the variation observed in frequency of acute myocardial infarction and out-of-hospital death,\(^16-19\) suggesting that a common underlying mechanism couples transient ischemia with these morbid events, or at least is shared by these events. The frequency of ambulant ischemic activity increases shortly after waking, peaks around noon, plateaus in the afternoon, and is at its lowest late in the night and in the early morning hours. The exception is the relatively infrequent patient with Prinzmetal's variant angina, who has peak ischemic activity in the early morning, often at approximately 2:00-3:00 AM.\(^20\) In the more commonly seen patients with stable effort angina, the morning increase in ischemic activity is closely linked to the morning increase in heart rate.\(^21\) Furthermore, it has been suggested that \(\beta\)-adrenergic activity is at least one important inciting factor because \(\beta\)-receptor blockers attenuate and essentially eliminate the morning surge in both heart rate and ischemic activity.\(^21\) Dihydropyridine calcium antagonists also reduce daily ischemic activity but do not appear to alter its circadian characteristics.\(^22\) Ischemia that is eliminated by \(\beta\)-blockade has the major component of its power spectrum concentrated in a bandwidth that approximates 24 hours. Ischemia that recurs after \(\beta\)-blockade has its major component in a bandwidth that approximates 5-8 hours. These different power spectrum signatures suggest that there may be different mechanisms involved in the residual ambulant ischemia that occurs after \(\beta\)-blockade. Although this is interesting and helps to clarify the pathophysiology of out-of-hospital ischemia, the central importance of these findings depends on whether silent episodes have prognostic importance.

**What Are the Prognostic Implications of Ambulant Ischemia?**

In addition to its high frequency and shared circadian distribution with morbid coronary disease events, there is strong evidence indicating that silent ischemia does have prognostic importance. Initial data came from studies of patients with unstable angina where multiple reports support a strong association between silent ischemia and outcome.\(^7-9,15,23-25\) In these stud-
ies, the risk of death was increased approximately fourfold to ninefold in patients with silent ischemia recurring during medical therapy, which controlled angina compared with patients who had no detectable recurrent ischemia. The risk of nonfatal infarction or death was increased approximately 20-fold in one report.9

Recently, reports dealing with the risk of adverse outcome and ambulant ischemia in patients with clinically stable chest pain syndromes have emerged.1,25–29 In these reports, the largest and most complete of which appears in this issue of Circulation,29 the presence of ambulant ischemia was associated with a twofold to fourfold increase in risk of death. The risk of nonfatal infarction or death was increased approximately 14-fold in one study.27 Because outcome in coronary artery disease patients is multifactorial, multivariate analysis was used in three studies.8,27,29 In each study, silent ischemia was the best independent predictor of outcome among a number of factors that included coronary angiography and exercise test results. It should be emphasized that all these studies are of patients with coronary artery disease.

What About Antianginal Treatment?

Antiangular agents, such as nitrates,2 β-blockers,30 and calcium antagonists,22,31 reduce or prevent silent ischemia. Several large studies, including the Deedwania report in this issue,29 identified a significant proportion of patients who appeared symptomatically stable during treatment with antiangular agents yet continued to have recurrent ambulant ischemia, most of which was silent. Mulcahy et al32 found that approximately one third of their 114 patients receiving antiangular treatment had silent ischemia. Those patients in Canadian class I and II for angina, which was well-controlled by antiangular treatment, had the same frequency and duration of silent episodes as those who were poorly controlled with class III and IV symptoms. Thus, well-controlled symptoms do not necessarily predict the absence of recurrent ambulant ischemia. Most patients who had recurrent ischemia were in the subset of patients with abnormal exercise tests. Another recent report of 325 patients monitored while receiving antiangular treatment also suggested that approximately 40% of those taking antiangular agents continued to have ambulant ischemia.33 The largest proportion of patients who had ambulant ischemia and those with the most frequent episodes were the patients with abnormal exercise test results. A small percentage of patients with negative test results also had silent ischemia. In the current report, Deedwania and colleagues29 found recurrent ischemia in approximately 40% of their patients receiving antiangular treatment. These three provocative reports indicate that ambulant ischemia, most of which is silent, may continue to occur in a significant proportion of symptomatically stable patients receiving what was thought to be effective antiangular treatment.

<table>
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<tr>
<th>Table 1. Current Knowledge About Ambulant Myocardial Ischemia</th>
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<td>Recurrent ischemia, most of which is silent, detected by ambulatory ECG monitoring is associated with increased risk of adverse outcome.</td>
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<td>Therapy directed toward symptom control may be insufficient to control silent ambulant ischemia.</td>
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<td>Antiangular agents can control symptomatic and silent ischemia but monitoring is needed.</td>
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Knowledge is lacking as to whether a strategy of detection and treatment based on ischemia, per se, is associated with reduced adverse outcome.

What Is Known and Where Do We Go From Here?

While a number of questions remain unanswered and more data are desired, it is helpful to summarize what is known at this point relative to silent ischemia (Table 1). It seems reasonable to conclude that recurrent ischemia, most of which is silent, may be detected by ambulatory ECG monitoring, exercise testing, thallium 201 imaging, or left ventricular imaging in a large proportion of patients within all the clinical syndromes of coronary artery disease. There is now substantial evidence to support the notion that this recurrent residual ischemia is associated with a significant increase in risk of adverse events. While antiangular treatment can control the symptomatic and reduce the silent ischemic episodes, therapy directed towards symptom control may be insufficient to control recurrent silent ischemia in many of these patients. Thus, testing to detect residual silent episodes is needed if these episodes are used to assess prognosis. Knowledge is clearly lacking at this time as to whether a strategy of detection and treatment based on identification of ischemia is of value in reducing the risk of adverse outcome. Additional advances in this area will require large, well-controlled clinical trials.

References

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